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PEDAGOGICAL CLINICAL PROBE ON APPROACH OF DRUG THERAPIES USED FOR COMBATING BREAST CANCER

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ABSTRACT

Now these days, breast cancer is the most common invasive cancer occur in females which are diagnosed as ductal carcinoma and lobular carcinoma. It also occurs in males, however it is more prevalent in females and quite rare in males but incidence trends are same for both genders. It is one of the leading causes of mortality in many developing countries and has a high incidence rate in developed nations including England, Japan, US and many other European countries. Since, developed nations have availability of improved medication and early diagnosis of the disease; mortality rates are lower in developed nations as compared to less-developed or developing nations. The risk factors include gender, age, genetics, diet, hormonal levels, radiation, use of certain oral contraceptives, breast-feeding, certain environmental pollutants and type II diabetes have been associated with occurrence of breast cancer. BRCA1 and BRCA2 gene mutations are also responsible for hereditary breast cancer. Major signs and symptoms are lump formation, skin dimpling around the breast; change in the color and texture; sometimes clear or bloody fluid leaking from the nipples. Diagnosis and screening of the disease is mostly done using histopathological studies, biopsy and mammography. Various therapies including chemotherapy, radiation, surgical removal, antiestrogen therapy and ovarian suppression have been used to treat breast cancer. With new advanced medical technology, new device is going to invented for specific or targeted drug therapies that would have least side effects and higher success rate used in the treatment of breast cancer. Hence, this brief approach is perceptive review to enumerate various available drug targeted therapies involving the use of drug delivery systems or vehicles like liposomes, antibody-drug conjugates and other nanoparticles to carry the cytotoxic drug to the drug target approved by FDA while many are still under clinical trials to combat the breast cancer.

KEYWORDS: Breast Cancer, BRCA Mutation, Antiestrogen Therapy, Ovarian Suppression, Mastectomy

INTRODUCTION

Breast cancer is a heterogeneous disease in terms of gene expression, morphology, clinical course and response to treatment.[1] Worldwide, more than one million women are diagnosed with breast cancer every year and approximately, more than 410,000 death caused from the disease representing 14% of female cancer deaths.[2] Breast cancer in men is rare, accounting for approximately 1% of breast cancer cases in the US. It was diagnosed with breast pain; persistent changes in the shape of breast, such as swelling, thickening, or redness of the breast's skin and nipple abnormalities such as spontaneous discharge (especially if bloody), erosion, inversion, or tenderness.[3,4] Potential risk factors which are commonly associated with breast cancer include gender and old age[5], genetics, lack of childbearing or lack of breastfeeding[6], higher levels of certain hormones, obesity, alcohol and tobacco consumption, use of oral contraceptives, radiation and some environmental pollutants.[7] Previous reports have demonstrated that 20% of risk chances of occurrence

of breast cancer may be associated with type II diabetes.[8] Earlier reports was suggested that gene mutations in BRCA1 and BRCA2 were responsible for the majority of hereditary breast cancers, although more recent studies have demonstrated that mutations in the two genes only account for 25–28% of the family risk.[9] Other significant mutations include: p53 (Li–Fraumeni syndrome), PTEN (Cowden syndrome), and STK11 (Peutz–Jeghers syndrome), CHEK2, ATM, BRIP1, and PALB2.[10] Various techniques are now available for screening and early detection of breast cancer e.g. mammograph, magnetic resonance imaging (MRI), clinical breast examination and breast ultrasound. Breast cancer is usually treated by chemotherapy, radiotherapy and surgery. Surgical treatment used for breast cancer are breast-conserving surgery (BCS) and mastectomy.[3,11] Adjuvant therapies are frequently used to treat breast cancer varying from chemotherapy, antiestrogen therapy, ovarian suppression, or a combination of them to combat breast cancer to reduce the mortality rate. [12]

BREAST CANCER: PREVALENCE

Future estimates of mortality rate has crucial role for communication, prevention and anticipation related to the socio-ecomonic burden of diseases and for developing scenarios studying the effects of reducing its environmental exposure.[13] Globally, 1.4 million cases of breast cancer cases are diagnosed each year and approximately one-third died because of the disease due to lack of getting awareness and effective treatments. [14] It is also a potentially one of the most curable cancer among other cancers with reported 5-year relative survival rates currently cover a 7-fold range based on analysis of data of 13% in Gambia, 31%-54% in India, 40% - 55% in the Philippines, 46% in Uganda, 57%-66% in Thailand, 57%-81% in South Korea, 58% in Zimbabwe, 58%- 90% in China, 70% in Cuba and Costa Rica, 77% in Turkey, 60%-80% in Europe and 92% in the USA due to early prognosis and getting safe therapy as well as timely medication used for its treatment.[15] Available data was suggested that breast cancer in younger women represents a significant burden in developing countries with more than 20% of mortality.[16] Recently, more than one million new cases of breast cancer reported and about 600000 deaths caused by it are being reported annually with reduced mortality rate.[17] National control plans (NCCPs) are effective tools of raising awareness, prevention, screening, diagnosis, management and control of cancer in every individual country depending on its local epidemiology and resources.[18] The first priority was found to be reported to reduce mortality rate to treat the breast cancer in any country via breast conserving surgery or mastectomy along with effective adjuvant treatment.[15] Breast cancer mortality in developed countries are defiantly lower as compared to developing countries due to early diagnosis and availability of improved medication in the U.S [19,20]. Improved therapeutic efficacy may be involved in the decrease in the mortality rate in the US after 1990, because there was improvement in survival rates in addition to the benefit of early detection by screening and early treatment after screening.[21] In Japan, deaths of 11918 women were reported due to breast cancer in 2009, leading to an age-adjusted mortality rate of 11.8 per 100000 population and also the incidence of breast cancer may be increasing over the next few decade.[22] While, in United Kingdom, survival rates were quite differ between socioeconomic and ethnic groups with geographical distribution and despite the increase of survival rate from 74.8% to 81.6% between 1995 to 2007.[23,24] The highest incidence rates occur in the most developed regions of the world, with 74.1 new cases per 100000 women in comparison to the 31.3 new cases per 100000 observed in less-developed regions but still the mortality rates are actually higher in developing countries.[19,25] Incidence rates has increased by 50-100% in some Asian countries including India and China during the last two decades.[26,27] The life time risk caused by breast cancer among all Iranian women in 2005-2007 was 12.5% with 24.4% occurrence among others prevalent malignancy with high expenditure of its treatment as compared to its cost effective medical therapies used in late-stage treatment in Latin and North America followed by Africa and

Asia.[28-30] As per the ICMR-PBCR data, breast cancer is the commonest cancer among women in urban registries of Delhi, Mumbai, Ahmedabad, Kolkata, and Trivandrum has been seen across all regions of India and in all age groups but more so in the younger age groups below 45 years.[31,32] Breast cancer was reported the fifth cause of death from cancer overall approximately 458 000 deaths and estimated 189,000 deaths is almost equal to the estimated number of deaths from lung cancer (188,000 deaths. [33]

BREAST CANCER: DIAGNOSIS

Various diagnostic methods are being used for the breast cancer such as conventional intraoperative hematoxylin, eosin (HE) staining, cytokeratin immunohistochemistry (CK-IHC) were performed to detect potential sentinel lymph node (SLN) metastasis in breast cancer.[34] As well as, high resolution melting has been used to screen exon 11 from 71 breast cancer patients in Morocco using conventional Sanger sequencing to confirm the presence of possible mutations [35]. Immunomagnetic separation (IMS) technology has been found to have higher sensitivity and specificity which makes it an effective and feasible intraoperative detection method of sentinel lymph node (SLN) for breast cancer diagnosis.[34,35] Lecitin histochemistry has also been used as a prognostic carbohydrate-dependent probe for invasive ductal carcinoma of the breast [36].

BREAST CANCER: NEW TARGETED THERAPIES

Used current strategies in breast cancer therapy are classical chemotherapy, hormone therapy, and targeted therapies which are usually associated with chemo-resistance and serious adverse effects.[37] The emergence of nanotechnology has made a significant impact on clinical therapeutics in the last two decades as the advances in biocompatible nanoscale drug carriers such as liposomes and polymeric nanoparticles have enabled more efficient and safer delivery of a myriad of drugs.[38] Delivery of the encapsulated chemotherapeutic is based on controlled release in the tumor microenvironment, followed by the subsequent cellular uptake of the free drug, small molecule drugs or gene medicines such as antisense oligonucleotides and angiogenesis inhibitors which are be added to chemotherapy or to radiotherapy, or used in combination with immunotherapy or vaccine therapy.[39-41] Tyrosine kinases are important role in cell proliferation and cell differentiation which are now proposed to be used in the pathophysiology of cancer and its receptors might be used to block cell signaling.[42,43] Vaccines constitute an active and specific immunotherapy designed to stimulate the intrinsic anti-tumor immune response by presenting tumor-associated antigens (TAAs) expressed on normal tissues which are over-expressed on tumor cells.[44-46] Overexpression of some oncogenes such as *HER*-2 (c-*erbB*-2, *Neu*), *bcl*-2/*bcl*-xL, protein kinase A (PKA) and transferrin receptor gene (*TfR* gene) with specific modification as growing repertoire are significantly under inventive consideration to be used for the prognosis of breast cancer.[47,48] Matrix metalloproteinases (MMPs) and Curcumin (diferuloylmethane) were chemically and genetically modified for their operational down-regulation and up-regulation respectively which were further used to study their role as diagnostic markers and drug targeted delivery to control metastasis.[49,50]

BREAST CANCER: DRUG DELIVERY SYSTEMS

Targeted drug delivery usually involves surface modifications made in the nano-carriers in which therapeutic agents can be embedded, encapsulated, or even adsorbed or conjugated to increase the aqueous solubility and stability of anticancer drugs and confer a degree of selectivity on their therapeutic effects along with their drug delivery systems e.g. liposomes, polymeric micelles and formulation of targeted polymer drug conjugates.[39,51,52] These targeted nanosystems

can be able to deliver drugs at targeted sites (across tumor's leaky vasculature and reach the tumor tissue) with site specificity and reproducibility in a passive or active way to achieve the goal of personalized cost-effective cancer therapy.[53,54-58] Liposomes have been formulated using naturally occurring and synthetic phospholipids with its unilamellar interior to provide the energy necessary to disperse the phospholipid molecules into the surrounding aqueous medium to load hydrophilic drugs, the phospholipid bilayer allows for the encapsulation of hydrophobic chemotherapeutics upto loading of 10^4 drug molecules per liposome particle.[38,59-63] Her2/neu (CD340) were reported upregulated in 30% in breast cancer pateints to control the cancerous cells and Trastuzumab-conjugated Lipo[MNP@*m*-SiO2] was found to be a potential tool for this targeted drug delivery in Her2/*neu*-positive breast cancer.[64] Lapatinib is a dual inhibitor of EGFR (epidermal grwoth factor receptor) and human epidermal growth factor receptor2 (HER2) which was previoulsy used to treat breast cancer at advanced stage.[65] In another study, for the first time the combination of sulfatide and lipid perfluorooctylbromide NPs was used in targeted breast cancer delivery vehicle for paclitaxel (PTX) for breast cancer treatment.[66] VIP-SSMM (vip-grafted sterically stabilized phospholipid mixed nanomicelles) could be used as an actively-targeted nanosized drug delivery platform for breast cancer cells over-expressing VIP receptors.[67] While, AS1411 aptamer-functionalized liposomes, cholesterol-modified DNA strands bound liposomes and unimolecular micelles formed by dendritic amphiphilic block copolymers were also reported to be used to recognize nucleolin overexpressed on MCF-7 cell surface, and therefore enable drug delivery with high specificity nd selectivity.[68-70] The use of biologically and chemcially modified polymers as scaffolds in the nanoparticle formulation was found helpful to simplify the composition and providing more spatial arrangemnet for laoding carrier for multiple functionalities intend to strive for future development of nanotechnology for in-vitro and in-vivo breast cancer therapeuti managemnt especially including anti-HER2/neu antibody trastuzumab (Herceptin).[71,72] Modified hyperbranched dendrimers, globular proteins and serum albumin having spherical nanocarriers were dveloped for loading methotrexate and noscapine to form their conjuagtes that incorporated folic acid as a targeting agent to be found helpful for combating many human cancer have overexpressed folate receptors.[55,73-76] Antibody-conjugated drugs are also developed such as T-DM1 are still under clinical trails for comabting cancerous cells[77].

CONCLUSIONS

Hence, this detaild informative overview is quite helpful to get to aware the early onset of symptoms, prognosis, diagnosis and cost effective therapies used for medication of combating breast cancer. Effective diagnostic techniques which are coined for screening of breast cancer e.g. conventional intraoperative hematoxylin, eosin (HES) staining, cytokeratin immunohistochemistry (CK-IHC), Immunomagnetic separation (IMS) and Lecitin histochemistry (LHC) which have been used for their cost-effective, highly sensitive and highly reproducible results. As well as, more specific and targeted treatment therapeutic options were also found out including immunotherapy, Tyrosine Kinase-inhibitors, antisence therapy and Matrix metalloproteinase which might have higher accuracy and least as well as no side-effects as compared to used conventional non-targeted therapies. Targeted drug therapies are oftenly involve the use of nano-carrier based delivery systems which include liposomes, micelles, ligand, antibodies, dendriers and small peptides. These new advanced approachs are still going to be used as promising effective therapeutic tools to combat breast cancer with most efficacy,safe and site specific delivery vehicle as compared to previoulsy used costly conventional approaches.

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